

Clonidine for the Treatment of Agitation After Dexmedetomidine Discontinuation in Pediatric Patients: A Retrospective Cohort Study

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OBJECTIVE Dexmedetomidine has become a widely used drug in PICUs for sedation. We aim to determine the effects of clonidine on pediatric patients after dexmedetomidine use.

METHODS This was a retrospective cohort study that evaluated all pediatric patients admitted to a tertiary PICU who received dexmedetomidine infusion for >48 hours. Outcomes in patients exposed to clonidine (CLON) were compared with those of patients who were not exposed (NoCLON).

RESULTS A total of 216 patients were included in this study (43 CLON and 173 NoCLON). The primary outcome, agitation, was less in the CLON cohort (9.3%) than in the NoCLON cohort (9.3% versus 29.5%, respectively; $p < 0.01$). Hospital LOS was longer in the CLON group (59 versus 20 days, $p < 0.01$), as was PICU LOS (37.4 versus 11.1 days, $p < 0.01$). There was no significant difference in the occurrence of increased heart rate or blood pressure between the 2 cohorts. Patients exposed to concurrent midazolam and opioid infusions had higher incidence of agitation when they did not receive clonidine (CLON 8% versus NoCLON 37%, OR 0.15; 95% CI, 0.05–0.51; $p < 0.01$). In contrast, there was no difference in the incidence of agitation for the CLON group versus the NoCLON group when dexmedetomidine was administered alone (25% versus 19%, OR 1.4; $p = 0.99$).

CONCLUSIONS Our study confirms the importance and effectiveness of clonidine to treat agitation after dexmedetomidine discontinuation. A validated withdrawal scoring tool can help better define dexmedetomidine withdrawal in pediatric patients.

ABBREVIATIONS AUC, area under the curve of the receiver operating curve; bpm, beats per minute; CLON, clonidine-exposed cohort; IV, intravenous; LOS, length of stay; NoCLON, cohort not exposed to clonidine; PICU, pediatric intensive care unit; WAT-1, Withdrawal Assessment Tool

KEYWORDS agitation; clonidine; dexmedetomidine; pediatrics; sedation; withdrawal

J Pediatr Pharmacol Ther 2021;26(8):821–827

DOI: 10.5863/1551-6776-26.8.821

Introduction

Dexmedetomidine, a centrally and peripherally acting α_2 -agonist, has become a widely used drug in PICUs for sedation and anxiolysis, both in intubated and non-intubated patients. Studies have shown it to produce adequate sedation while causing minimal respiratory depression.¹ As its use increases, concerns regarding tolerance and dependence in pediatric patients are increasing, especially in patients exposed for a prolonged period. This can lead to withdrawal on discontinuation. Retrospective data in the critical care setting suggest concerns for rebound and withdrawal phenomena following 3 or more days of continued sedation with dexmedetomidine.² Withdrawal symptoms associated with prolonged use of dexmedetomidine include tachycardia, hypertension, increased agitation, insomnia, diarrhea, emesis, tremors, and increased secretions.² However,

a detailed dexmedetomidine withdrawal syndrome is yet to be defined in pediatric patients.

To prevent and treat withdrawal syndromes after prolonged exposure to continuous IV infusion of sedatives like opioids and benzodiazepines, many clinical providers will start enteral alternatives to allow transition off these infusions. This has been well studied in the pediatric population.^{3–5} Clonidine, another α_2 -adrenoreceptor agonist, is available enterally and has been studied in adults for its use to transition from dexmedetomidine, especially in terms of efficacy and cost-effectiveness.^{6,7} However, there are limited data evaluating the use of enteral clonidine to prevent withdrawal symptoms associated with the discontinuation of dexmedetomidine in pediatric patients. A nationwide survey of 147 pediatric intensivists revealed that 81% of those surveyed managed dexmedetomidine withdrawal symptoms with initiation of clonidine.⁸ In our study, we

aim to determine the effects of clonidine on pediatric patients after dexmedetomidine use. We hypothesize that patients exposed to clonidine after dexmedetomidine administration would have lower incidence of agitation than patients not exposed to clonidine.

Methods

Population. We performed a single center, retrospective observational cohort study conducted at a university-affiliated tertiary care children's hospital. Prior to data collection we obtained an exemption of review by the University of Texas Health Science Center at Houston Institutional Review Board to perform the retrospective chart review. Patients admitted at a 30-bed combined pediatric and cardiac intensive care unit from July 1, 2016, to July 1, 2019, were eligible to be included in the study. The inclusion criteria were patients younger than 18 years and who received dexmedetomidine infusion for at least 48 hours. Patients were excluded if they presented with neurological or psychiatric diagnoses (i.e., head trauma, intracranial hemorrhage, intentional overdose) at admission, received clonidine as a home medication, were transferred to an outside facility, or died while on dexmedetomidine. The cohort was divided into 2 groups on the basis of clonidine exposure: a clonidine-exposed group (CLON) with patients who were initiated on clonidine before or within 24 hours of dexmedetomidine discontinuation and a non-exposed group (NoCLON) that included patients who did not receive clonidine or received it 24 hours after discontinuation of the dexmedetomidine infusion.

Outcomes. The primary outcome was agitation. We defined agitation as documentation of "agitation" or "irritability" in the daily physician progress notes, associated with an intervention including benzodiazepines boluses or opioid boluses, between day 2 and day 7 after dexmedetomidine discontinuation. If there was no documentation of agitation, the following interventions were also included to meet the agitation outcome: restarting a dexmedetomidine drip, increasing the dose of the opioid infusion or benzodiazepine infusion, or using more than 2 consecutive boluses of benzodiazepine (IV or orally) and/or opioids (IV or orally), again between day 2 and day 7 after dexmedetomidine discontinuation.

Our secondary outcomes included total PICU LOS, hospital LOS, duration of invasive mechanical ventilation, and occurrence of increased heart rate and blood pressure. The hemodynamic changes were defined as change from baseline, measured 24 hours before the discontinuation of dexmedetomidine, to the values within the 24 hours after discontinuation of dexmedetomidine. Increased blood pressure, or simply hypertension, was defined as 2 measurements of 10 mm Hg above the baseline for systolic pressure or mean arterial pressure within the first 24 hours of discontinuation of dexmedetomidine infusion. Increased heart rate, or simply tachycardia, was defined as an increase in

the mean baseline of more than 15 beats per minute (bpm) within the first 24 hours after discontinuation of dexmedetomidine infusion.

Covariates. Demographic data collected included reason for admission (cardiac, patient admitted with congenital heart disease for management and/or surgery, versus non-cardiac), age, sex, and baseline weight (the average between admission and discharge weights). Patients were categorized into 5 age groups: newborn to 1 month, greater than 1 month to 2 years, greater than 2 years to 6 years, greater than 6 years to 13 years, and greater than 13 years to 18 years. Clinical data collected included duration of dexmedetomidine therapy in days, daily weight-based cumulative dexmedetomidine dose (mcg/kg/day), daily weight-based cumulative dose and duration of concomitant sedative and analgesic agents (i.e., fentanyl, hydromorphone, midazolam, methadone, and lorazepam) within 7 days of discontinuing dexmedetomidine, incidence of clonidine exposure, and starting dose of clonidine (mcg/kg/dose). Doses of fentanyl and hydromorphone were reported independently as well as total opioid infusion dose, using fentanyl equivalency (0.015 mg hydromorphone = 1 mcg fentanyl).⁹ The duration of opioid infusions has been combined as a single variable taking into consideration the duration of fentanyl and hydromorphone.

We included data on lorazepam and methadone doses if the patient received 3 or more consecutive doses that were initiated before discontinuation of dexmedetomidine. Any agents started after discontinuation were only included as meeting the definition of the primary outcome, incidence of agitation; as such, these doses would not have any impact as confounders for the outcome of agitation. Also despite these drugs' long half-life, 1 or 2 doses would not influence the outcome because steady-state would not have been achieved and the outcome of agitation was not evaluated until 24 hours after dexmedetomidine discontinuation. The route of lorazepam and methadone was not specified because lorazepam and methadone were converted by using a 1:1 ratio from IV to enteral routes.

Statistical Analysis. Patient characteristics and demographic data were reported as frequencies and percentages for categorical data and as means with standard deviation for continuous variables, with differences between cohorts assessed with chi-square or Fisher exact test depending on the sample size. These characteristics were compared with respect to the outcome of agitation to evaluate predictors, using Mann-Whitney *U* test for non-parametric continuous variables and Student *t* test for parametric variables. The outcomes in the CLON patients versus the NoCLON patients were compared by using appropriate statistical analysis: Fisher exact test for comparing agitation, Mann-Whitney *U* test for continuous variables, and chi-square test for analyses regarding the incidence of

Table 1. Patient Characteristics and Correlates of Clonidine Versus No Clonidine

	All (n = 216)	Clonidine (n = 43)	No Clonidine (n = 173)	p value
Age, mean \pm SD (median), mo	19 \pm 33 (5.3)	14.6 \pm 29	20.1 \pm 34	0.34
Age groups, n (%)				
0–1 mo	37 (17)	10 (23)	27 (16)	0.79
1 mo–2 yr	132 (61)	26 (60)	106 (61)	
2–6 yr	31 (14.5)	5 (12)	26 (15)	
6–13 yr	14 (6.5)	2 (5)	12 (7)	
13–18 yr	2 (1)	—	2 (1)	
Female, n (%)	101 (47)	15 (35)	86 (49.7)	0.09
Diagnosis: cardiac, n (%) [*]	78 (36)	20 (46.5)	58 (33.5)	0.15
Clonidine starting dose, mean \pm SD (range), mcg/kg/dose [†]	—	1.5 \pm 0.7 (0.5–4)	—	—
Dexmedetomidine duration, mean \pm SD, days	9.34 \pm 13.7	21.9 \pm 24	6.2 \pm 6.2	<0.001
Dexmedetomidine dose, mean \pm SD, mcg/kg/day [†]	2.60 \pm 1.5	3.08 \pm 1.4	2.48 \pm 1.5	0.02
Total opioid infusion duration, mean \pm SD, days	14 \pm 26 (n = 149)	31 \pm 45 (n = 38)	8 \pm 8 (n = 111)	<0.001
Fentanyl dose, mean \pm SD, mcg/kg/day [†]	49.1 \pm 32.1 (n = 149)	44.5 \pm 35.9 (n = 38)	50.6 \pm 30.7 (n = 111)	0.32
Hydromorphone dose, mean \pm SD, mg/kg/day [†]	0.99 \pm 1 (n = 26)	0.93 \pm 1 (n = 12)	1 \pm 1 (n = 14)	0.75
Midazolam duration, mean \pm SD, days	11 \pm 19 (n = 143)	23 \pm 31 (n = 39)	6 \pm 8 (n = 104)	<0.001
Midazolam dose, mean \pm SD, mg/kg/day [†]	2.39 \pm 3.6 (n = 143)	2.73 \pm 5.2 (n = 39)	1.3 \pm 2.3 (n = 104)	0.07
Lorazepam duration, mean \pm SD, days	23 \pm 37 (n = 99)	44 \pm 55 (n = 33)	13 \pm 15 (n = 66)	<0.001
Lorazepam dose, mean \pm SD, mg/kg/day [†]	0.23 \pm 0.2 (n = 99)	0.19 \pm 0.24 (n = 33)	0.09 \pm 0.18 (n = 66)	0.001
Methadone duration, mean \pm SD, days	24 \pm 29 (n = 74)	35 \pm 39 (n = 32)	16 \pm 15 (n = 42)	0.006
Methadone, mean \pm SD, mg/kg/day [†]	0.27 \pm 0.2 (n = 74)	0.2 \pm 0.17 (n = 32)	0.07 \pm 0.16 (n = 42)	<0.001

^{*} Cardiac defined as patient admitted to the PICU with congenital heart disease for management and/or surgery.

[†] All drug doses were the cumulative dose of the drug given per weight over its duration of administration.

increased systolic blood pressure and increased heart rate from baseline. Multivariable logistic regression analysis was used to identify significant predictors of agitation. Factors significant in univariate analysis were entered in the initial model, and the final model was generated by stepwise procedure. Hosmer-Lemeshow test was used to assess the goodness-of-fit of the final model, and AUC was used to determine the classification accuracy of the final model. Statistical tests were performed with IBM SPSS Statistics (IBM SPSS Statistics for Windows, version 24.0, IBM Corp, Armonk, NY). Statistical significance was notated by a p value of 0.05.

Results

The chart review yielded a total of 43 CLON patients and 173 NoCLON patients, an approximate 1:4 distribution between the 2 groups. Patient characteristics and correlates of the 2 groups are compared in Table 1. Most

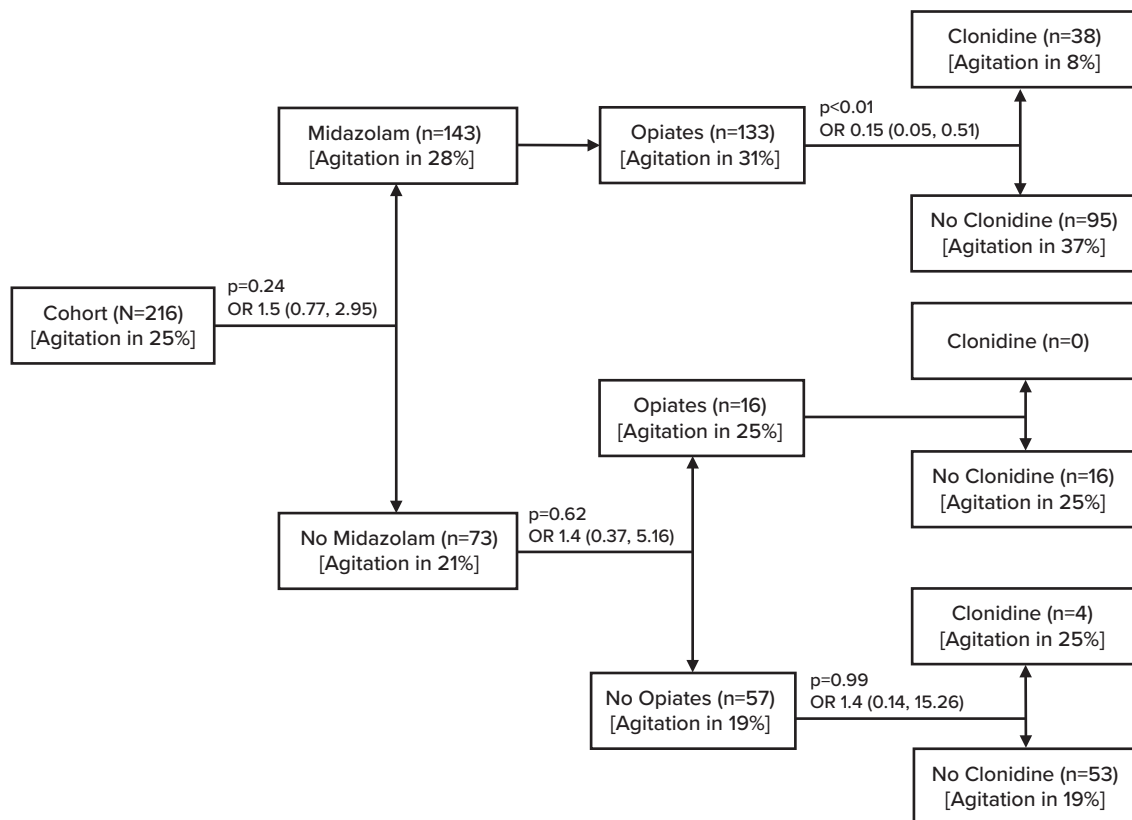
of our patients were in the age group of 1 month to 2 years (61%). There were no significant differences in age, sex, and primary diagnosis between the 2 groups. CLON patients did have significantly increased dexmedetomidine total dose (3.08 versus 2.48 mcg/kg/day, $p = 0.02$) and duration (21.9 versus 6.2 days, $p < 0.001$). The 2 groups had similar exposure to opioid and midazolam infusions, but CLON patients had higher total doses of enteral methadone (0.2 versus 0.07 mg/kg/day, $p < 0.001$) and lorazepam (0.19 versus 0.09 mg/kg/day, $p = 0.001$). Supplemental Table 1 analyzes patient characteristics and predictors with respect to agitation.

The outcome of agitation in clonidine-exposed versus non-exposed patients is presented in Table 2. The occurrence of agitation was lower in the CLON cohort (9.3%) than the NoCLON cohort (29.5%) ($p < 0.01$), supporting our hypothesis. The secondary outcomes hospital LOS and PICU LOS were longer in the CLON group

Table 2. Primary and Secondary Outcomes Association With Clonidine Exposure (N = 216)

	Clonidine (n = 43)	No Clonidine (n = 173)	p value
Agitation, n (%)	4 (9.3)	51 (29.5)	<0.01
Hospital LOS, mean ± SD, days	59 ± 63.7	20 ± 20.8	<0.01
PICU LOS, mean ± SD, days	37.4 ± 38.1	11.1 ± 11.5	<0.01
Invasive MV duration, mean ± SD, hr (n = 144)	954 ± 1283 (n = 35)	169 ± 214 (n = 109)	<0.01
Tachycardia, n (%)	14 (32.6)	75 (43.4)	0.19
Hypertension, n (%)	23 (53.5)	91 (52.6)	0.91

MV, mechanical ventilation

Figure. Decision tree diagram for primary outcome, agitation.

p values calculated with Fisher exact test. Results are expressed as OR and 95% confidence interval.

(59 versus 20 days, $p < 0.01$ and 37.4 versus 11.1 days, $p < 0.01$, respectively). Invasive mechanical ventilation duration was also significantly longer in CLON patients (954 hours versus 169 hours, $p < 0.01$). There was no significant difference in the occurrence of tachycardia or hypertension between the 2 groups.

The Figure displays a decision tree diagram that looks at the incidence of agitation in the entire dexmedetomidine-exposed cohort, based on exposure to opiates and midazolam. Patients exposed to both

midazolam and opiate infusions who did not receive clonidine had a significant association to agitation (CLON 8% versus NoCLON 37%, OR 0.15; 95% CI, 0.05–0.51; $p < 0.01$). In contrast to patients who received only dexmedetomidine with no exposure to opiates or midazolam, there was no significant difference in agitation between the CLON cohort and the NoCLON cohort (25% versus 19%, OR 1.4, $p = 0.99$).

The results of the multivariable logistic regression analysis are summarized in Table 3 (Hosmer-Lemeshow

Table 3. Multivariable Logistic Regression Model for the Outcome of Agitation*

	Univariate Analysis Odds Ratio (95% CI)	Multivariable Analysis (Final Model) Odds Ratio (95% CI)	p value
Age group	0.97 (0.65–1.41)	Not included in the model	—
Sex	1.25 (0.68–2.31)	Not included in the model	—
Ventilator duration	1.00 (1.00–1.00)	Not included in the model	—
Cardiac patient	1.13 (0.59–2.11)	Not included in the model	—
Opiate infusions			
Daily total dose/weight	1.01 (1.00–1.02)	Eliminated with stepwise procedure	—
Length of treatment, days	1.0 (0.98–1.01)	Not included in the model	—
Midazolam infusion			
Daily total dose/weight	1.15 (1.01–1.31)	1.12 (1.01–1.24)	0.04
Length of treatment, days	1.00 (0.98–1.02)	Not included in the model	—
Dexmedetomidine			
Daily total dose/weight	1.01 (0.89–1.16)	Not included in the model	—
Length of treatment, days	1.00 (0.97–1.02)	Eliminated with stepwise procedure	—
Methadone			
Exposure	2.59 (1.38–4.87)	2.12 (0.88–5.14)	0.09
Daily total dose/weight	5.44 (1.06–28.03)	Not included in the model	—
Lorazepam			
Exposure	3.76 (1.95–7.24)	3.83 (1.7, 8.64)	0.001
Daily total dose/weight	7.07 (1.52–32.94)	Eliminated with stepwise procedure	—
Clonidine			
Exposure	0.25 (0.08–0.72)	0.07 (0.02–0.24)	<0.001

* Hosmer-Lemeshow p value = 0.60; AUC = 0.79 (95% CI, 0.72–0.87).

p value = 0.60; AUC = 0.79 [95% CI, 0.72–0.87]). The different factors were first tested in a simple logistic regression. Factors that were found to be significant in the univariate logistic regression were included in the initial multivariable model. These factors include opiate infusion dose, benzodiazepine infusion rate (total daily dose/weight), dexmedetomidine duration, use of methadone, use of lorazepam, daily dose of lorazepam, and use of clonidine. Stepwise elimination procedure was performed to obtain the final model. Factors included in the final model were midazolam infusion rate, use of methadone, use of lorazepam, and use of clonidine. Higher doses of midazolam and the use of lorazepam have higher odds of associated agitation. Use of clonidine has lower odds of associated agitation. In the Supplemental Tables 2 and 3, similar model analysis was performed in patients exposed to opiate infusions alone and in patients exposed to both opiate and midazolam infusions. Clonidine-exposed patients had lower odds of agitation after discontinuation of dexmedetomidine for each of these groups.

Discussion

Our cohort demonstrates that patients treated with clonidine, before or within 24 hours of dexmedetomidine discontinuation, have less occurrence of agitation

than patients not treated with clonidine. Our findings also confirmed that, in our cohort, patients with benzodiazepine infusions and interval doses of lorazepam have higher odds of having agitation. For that group of patients, clonidine-exposed patients have lower odds of having agitation.

Clonidine is being used frequently to switch to oral sedation from IV dexmedetomidine and prevent hypothetical dexmedetomidine withdrawal. In our cohort, patients exposed to clonidine had a lower incidence of agitation. The use of clonidine was more frequent in patients with higher dexmedetomidine dose and longer length of therapy, and also higher lorazepam, midazolam, and methadone dose, as presented in Table 1. This difference was evaluated in the multiple regression analysis presented in Table 3 and Supplemental Tables 2 and 3. As presented in the multivariable logistic regression analysis, total dexmedetomidine dose and duration did not have any direct impact on agitation or affect the effect of clonidine to prevent agitation. A retrospective descriptive study by Lardieri et al² looked at 19 pediatric patients receiving dexmedetomidine for >5 days, with 12 receiving clonidine. The 2 groups, clonidine versus no clonidine, showed no difference in Withdrawal Assessment Tool (WAT-1) scores (p = 0.49), but patients in the clonidine group did have a lower average heart rate (112

bpm with range, 88.5–151.5 versus 138.4 bpm with range, 117–168.3; $p = 0.003$).² We did not incorporate a sedation score because we only use such scores (i.e., COMFORT Behavior Scores) for intubated patients, and not all the patients in our study were intubated at the moment of dexmedetomidine discontinuation. Another retrospective observational pediatric study ($n = 115$) comparing 27 patients receiving clonidine with 88 who did not receive clonidine showed no difference in withdrawal symptoms between groups (71.6% versus 63%, $p = 0.394$); in addition, patients exposed to clonidine had higher PICU LOS (23.5 versus 10.0 days, $p < 0.001$).¹⁰ This last result is similar to our findings. In terms of directly comparing dexmedetomidine versus clonidine, one adult study showed similar efficacy between dexmedetomidine and clonidine while having a potential drug acquisition cost avoidance of \$819 to \$2338 per patient.⁶ Another adult study revealed similar Richmond Agitation Sedation Scale and Confusion Assessment Method scores, along with no difference in rates of hypotension, between parental dexmedetomidine and enteral clonidine.⁷ The direct comparison between dexmedetomidine and clonidine in the pediatric literature is sparse.

In our cohort, patients exposed to clonidine have longer time of admission in the hospital and PICU. They also had longer time on invasive mechanical ventilation. These results are probably explained by the retrospective design, and they reflect that clonidine is used in patients with prolonged admissions. In addition, patients exposed to clonidine were treated with dexmedetomidine for longer times than patients not treated with clonidine (21 days versus 6 days, $p < 0.001$). It was likely that the decision to start clonidine occurred for patients with longer times of dexmedetomidine infusion as there was no set protocol at our institution, despite this practice not being well studied to date. PICU providers in our center are inclined to initiate clonidine in patients with high sedation requirements who need escalating infusion rates, and/or numerous intermittent bolus doses. A prospective study with protocolized time to start clonidine is necessary to determine all the benefits of clonidine as dexmedetomidine withdrawal treatment.

The definition of dexmedetomidine withdrawal has not been validated as a score. Therefore, it is exceedingly difficult to use a specific measure of dexmedetomidine withdrawal as an outcome in pediatric patients. We decided to use agitation as the primary outcome after the discontinuation of dexmedetomidine without incorporating changes in vital signs as tachycardia and hypertension. The outcome of agitation was a comprehensive composite of physician assessment of that diagnosis and an intervention or documentation of medical intervention in the medication administration record. When evaluating covariates that can generate specific withdrawal syndromes, only the use of benzodiazepines, infusion and intermittent doses, appears to be associated with agitation. Using multivariable logistic regression, higher doses

of midazolam infusion and use of lorazepam were both independent predictors of agitation (OR 1.12, $p = 0.04$ and OR 3.82, $p = 0.001$ respectively). Benzodiazepines have long been established to be associated with withdrawal symptoms, including agitation.^{3,5} The decision tree diagram in the Image reveals that patients who are exposed to multiple sedative and analgesic medications (i.e., opiates, midazolam, dexmedetomidine) appear to benefit most from clonidine in reducing agitation after discontinuation of dexmedetomidine (OR 0.15, $p < 0.01$). This benefit was not present when looking at patients receiving only dexmedetomidine without other sedatives.

In our study, no significant difference existed between the occurrences of increased heart rate or blood pressure. This needs to be further evaluated, because tachycardia and hypertension are part of dexmedetomidine withdrawal symptomatology.^{11–13} One extreme example in a case report discussed a pediatric patient without heart disease who experienced supraventricular tachycardia 12 hours after discontinuation of a dexmedetomidine infusion of 10 days.¹⁴ In our study, there was no difference between the heart rate or blood pressure before and after discontinuation of dexmedetomidine. We plan to validate prospectively a dexmedetomidine withdrawal score incorporating changes in vital signs along with agitation.

The limitations of our study reside in the retrospective design. There was disparity in the patients who received clonidine and the concomitant sedation therapies. As described, other assessments could have been incorporated into the study but were missing in most of the charts (i.e., WAT-1 scores). This number would have helped assess the overlap of opioid and benzodiazepine withdrawal. However, these medications were incorporated in our regression model, and only benzodiazepines were associated with higher odds of agitation. A score like the Pediatric Risk of Mortality score, that was not readily available in the records during the time of study, could help stratify the patients on the basis of severity of illness. This stratification could further reveal the effects of clonidine on patients with varying severity of illness. Our study sample was powered for the primary outcome of agitation. The non-significant association with tachycardia and hypertension must be further investigated in a larger population study. When adding tachycardia and/or hypertension to the outcome of agitation to define withdrawal in our cohort, lower number of patients who received clonidine had withdrawal than did patients not exposed to clonidine (62.8% versus 81.5%, $p = 0.008$).

Conclusion

Our findings confirm the importance and effectiveness of clonidine to treat agitation after dexmedetomidine discontinuation. Dexmedetomidine, given its safe side-effect profile compared with that of other sedatives, has seen growing widespread usage among PICU providers. With increasing usage, we need to be able to effectively

diagnose and treat withdrawal associated with dexmedetomidine. In our whole cohort of patients who received dexmedetomidine, clonidine appears to decrease the incidence of agitation. To better evaluate withdrawal in pediatric dexmedetomidine use, a validated withdrawal scoring tool is needed. Prospective randomized control trials can further reveal the utility of clonidine for patients in this population.

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Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Ethical Approval and Informed Consent. This study was approved by University of Texas Health Science Center at Houston Institutional Review Board. Given the nature of this study, informed consent was not required.

Acknowledgments. Pediatric critical care physicians, advanced practice providers, pharmacists, and medical teams at Children's Memorial Hermann Hospital for their assistance. Preliminary results were presented at the Society of Critical Care Medicine Critical Care Congress Conference in Orlando, FL, on February 16, 2020.

Submitted. December 14, 2020

Accepted. February 2, 2021

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